CPAG Summary Report for Clinical Panel – URN 1735 Selexipag for treating pulmonary arterial hypertension (PAH) in adults

The Benefits of the Proposition			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	There is no survival benefit [B]	The main study (Sitbon et al. 2015, n=1,156) measured death up to the end of the study both specifically due to PAH, and also due to any cause. When compared with placebo there was no statistically significant difference in either death from any cause (hazard ratio (HR) 0.97, 95% confidence interval (CI): 0.74 to 1.28, p=0.42) or death due to PAH (HR 0.86, 95% CI: 0.63 to 1.18, p=0.18. The results suggest that there is no statistically significant difference between the 2 groups for either mortality outcome. The authors stated these results should be interpreted as exploratory because people may have received other treatments for PAH, including some people in the placebo group receiving selexipag, which may affect the treatment effect. Also the European public assessment report (EPAR) stated that the mortality data is complex to assess, with some results showing selexipag had a negative effect, a neutral affect, and a best case scenario positive effect of up to a 25% reduction, on mortality. They noted that these models should, however, be interpreted with caution because in any such model assumptions have to be made.
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	

7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [B]	<u>All adverse events</u> The main study (Sitbon et al. 2015, =1,156) stated that 43.8% (n=252) of people receiving selexipag and 47.1% (n=272) of people receiving placebo reported ≥1 serious adverse events. A statistically significantly higher proportion of people stopped taking selexipag due to adverse events compared with placebo; 14.3% (n=82) and 7.1% (n=41) respectively (p<0.001). The most frequent adverse events leading people to stop taking selexipag were headache (3.3%), diarrhoea (2.3%) and nausea (1.7%). Death from any cause was 28 patients (4.9%) in the selexipag group and 18 patients (3.1%) in the placebo group. The results from the study suggest that most people treated with selexipag may experience an adverse event with around 14% experiencing a serious adverse event leading to stopping treatment. Results should be interpreted with caution because some people were not on any background treatments, and others were on varying, locally determined background therapies before starting additional treatment with either selexipag or placebo. This may disguise the true effect of selexipag on adverse events.
11.	Delivery of intervention	Not measured	

Other health outcome measures determined by the evidence review			
No	Outcome	Grade of evidence	Summary from evidence review

	measure		
1.	Composite of death or complication related to pulmonary arterial hypertension (PAH)	Grade B	This composite outcome is a combination of clinical events that might happen including hospitalisation, disease progression, and death from any cause, where any one of those events would count as part of the composite. Patients with PAH have an increased risk of morbidity and mortality. Sitbon et al. (2015) showed that selexipag statistically significantly reduced the risk of the composite outcome occurring when compared with placebo 26 weeks after starting treatment, with a rate of 27.0% for selexipag compared with 41.6% for placebo, HR 0.60 (99% CI: 0.46 to 0.78) p<0.001. The evidence suggests that selexipag results in a lowering in the risk of a morbidity or mortality event occurring. This result was supported by a sub group analysis study; Gaine et al. (2017) for people with PAH associated with connective tissue disease. Results should be interpreted with caution because the study authors noted that the composite outcome contains a number of subjective components (although steps were taken to address this weakness, including adjudication by a blinded 3-person panel). Also, although the use of a composite mortality/morbidity outcome is "encouraged" by the EMA in PAH, the EPAR stated that the outcome made it difficult to assess the true effect on all-cause mortality.
2.	Pulmonary vascular resistance (PVR)	Grade B	PAH causes the tiny arteries in the lungs to become narrow or blocked making it harder for blood to flow through them. PVR is the resistance that must be overcome to push blood through the pulmonary circulatory system and create flow. Simonneau et al. (2012) showed a statistically significant reduction in PVR at 17 weeks follow-up for patients receiving selexipag compared with placebo, with an average treatment effect of -33% (95% CI

			-47 to -15.2) p=0.0022. This result was supported by Tanabe et al. (2017). The evidence indicates that receiving selexipag reduces the resistance in these arteries by somewhere between 15.2 to 47%, which will allow increased blood flow, a reduction in lung blood pressure, alleviation of the symptoms of PAH, and a reduction in the risk of heart failure. Evidence should be interpreted with caution because the studies are not sufficiently powered due to the number of people involved for statistical analyses and therefore be treated as descriptive only.
3.	6 minute walking distance (6MWD)	Grade A	6MWD measures the distance an individual is able to walk over a total of 6 minutes on a hard, flat surface. Symptoms of people with PAH include shortness of breath when undertaking mild exercise and the 6MWD test is a measure of how well patients can cope with this. Sitbon et al. (2015) reported a statistically significant improvement for selexipag of 12 metres (99% CI: 1 to 24), p=0.003 in median walking distance when compared with placebo at 26 weeks follow up. This result was supported by 2 smaller studies; Simonneau et al. (2012) (although the result was not statistically significant) and Tanabe et al. (2017). The evidence suggests that receiving selexipag statistically significantly improves the ability of patients to undertake mild exercise with improved functional capacity. Results should be interpreted with caution because values were assigned to 21.6% of patients in the study who could not be measured by the authors. This adds uncertainty to the finding because missing values were determined based on a criteria outlined within the study rather than on actual patient data.
4.	Change in WHO functional	Grade A	WHO functional class describes how severe a patient's pulmonary hypertension (PH) is. There are four

	class		different classes: I is the mildest and IV the most severe form of PH. Improvement in functional class indicates an improvement in the symptoms the patient is experiencing. Sitbon et al. (2015) reported no significant change in WHO functional class of patients (measured as an absence of worsening in functional class) when compared with placebo at 26 weeks follow up. Odds Ratio (OR) 1.16 (99% CI: 0.81 to 1.66) p=0.28. The evidence suggests that selexipag neither improves nor decreases the functional class of patients. This result was supported by 2 smaller studies; Simonneau et al. (2012) and Tanabe et al. (2017). Results should be interpreted with caution because values were assigned to 18.3% of patients in the study who could not be measured by the authors. This adds uncertainty to the finding because missing values were not based on actual patient data.